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Mitochondrial Fission and Fusion: A New Target for Cardiovascular Therapy?

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Mitochondria have long been recognized for their essential role in generating energy to sustain cardiac contraction. For years these organelles were viewed as static factories producing high energy phosphates, such as ATP, to power the heart and other organs. However, research over the last 15 years, beginning first in yeast and now in mammalian cells, has up-ended our understanding of mitochondria [1-4]. Mitochondria are thought to have arisen from the endocytosis of bacteria by other unicellular organisms, and these organisms managed to survive in a symbiotic relationship in the host cell [5]. Such a change is hypothesized to have occurred hundreds of thousands of years ago, and today mitochondria, although they contain DNA coding for 13 genes, are no longer anywhere near self-sufficient with many of their proteins encoded by nuclear DNA.

In the 1990's biologists discovered that yeast mitochondria rather than being static, undergo constant division (fission) and fusion, and that fission and fusion are essential for maintaining healthy mitochondria [1,3,6]. Loss of fission results in large networks of fused mitochondria, while excess fission leads to small, fragmented mitochondria. Furthermore, normal mitochondrial fusion is necessary for the stability of mitochondrial DNA [7]. Rather than occurring as isolated organelles in the cell, the mitochondria are interconnected and linked to cytoskeletal elements and inter-communicate. In mammalian cells there are 3 fusion proteins and 2 fission proteins identified to date. Mitofusin (Mfn) 1 and 2 fused the outer membrane of the mitochondria when two mitochondria join by fusion. Optic atrophy (OPA) 1 fuses the inner membrane, and also appears to have important functions linked to cristae structure and electron transport. Fission (Fis) 1 recruits Dynamin related protein (Drp)1 to the cell membrane, where Drp1 forms a multi-subunit belt around the cell leading to fission. Mutations in the fusion proteins have been linked to inherited neuropathies, including Charcot-Marie-Tooth disease.

Mitochondrial fission and fusion, described relatively recently and most extensively in yeast, occur constantly and are thought to be critical for normal mitochondrial function. In the yeast mitochondrial fusion and fission occur as frequently as every two minutes [8]. In contrast, in HeLa cells (a cancer cell line), fusion began within 2 h and all of mitochondria had undergone fusion by 12 h [9]. It is thought that fusion and fission occur at a much slower rate in primary mammalian cells, with a recent paper suggesting cardiac myocyte mitochondria may undergo fission and fusion only every 16 days [10]. If fission is interrupted, large networks of fused mitochondria occur. If fusion fails, the mitochondria become small and fragmented. Abnormalities in fission and fusion can lead to apoptosis [2,11], which is an important mechanism of cardiac myocyte loss in heart failure [12-14]. Thus, it is critical to maintain a symmetry between fusion and fission.

In the failing heart mitochondria are small and fragmented with loss of organization compared to normal hearts [15]. This change in mitochondrial morphology was associated with a decrease in OPA1 expression, both in a rat model of heart failure (high LAD ligation) and in end-stage failing human hearts with ischemic cardiomyopathy removed for transplant. No change in OPA1 levels were found in nonischemic cardiomyopathy. The fusion proteins, Mfn1 and 2, along with the fission protein, Drp1, were all increased in human ischemic and nonischemic failing hearts, suggesting an upregulation of fission and fusion in the failing heart. Thus, there were similarities between ischemic and nonischemic cardiomyopathy, but also distinct differences.

Conditional deletion of MFn1/Mfn2, which fuse the outer mitochondrial membrane, in adult mice leads to mitochondrial fragmentation, mitochondrial dysfunction and a rapidly progressive dilated cardiomyopathy [10]. If these genes are ablated in the embryo, the result is lethal to the embryo. In contrast, deletion of Mfn2 alone caused only mild changes in the heart [16]. The mitochondria were surprisingly larger and there was mild to moderate cardiac hypertrophy, with minor changes in cardiac function. Unexpectedly, deletion of Mfn2 was associated with better recovery from ischemia/reperfusion, possibly secondary to a reduction in reactive oxygen species (ROS) mediated mitochondrial depolarization. It is known that Mfn1 and Mfn2 can each compensate to a degree for the loss of the other, and this explains the absence of severe mitochondrial dysfunction with loss of Mfn2 [17]; however it does not explain the improved recovery from ischemia and the observed reduction in ROS.

Fragmented, small mitochondria have been found in cardiac disease. Can inhibiting fission be protective? Both heart failure and acute ischemia are associated with mitochondrial fragmentation [15]. Given that a balance between fission and fusion is critical for maintaining mitochondrial health and therefore cardiac myocyte health, it would seem plausible that inhibition of what appears to be excess mitochondrial fission would protect the heart. In an elegant and thorough study, investigators have shown exactly that Inhibition of expression of the fission protein, Drp-1, reduced cell death after simulated ischemia/reperfusion [18]. This treatment also reduced mitochondrial fragmentation and preserved long, tubular mitochondria. Furthermore, mitochondrial division inhibitor-1 (MDI-1), a pharmacologic inhibitor of Drp1, reduced mitochondrial fragmentation, reduced opening of the mitochondrial permeability pore, and reduced infarct size in a mouse model of myocardial ischemia.

Findings from this nascent field investigating mitochondrial fission and fusion in the heart suggest that this is a potential new

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set of targets for intervention to limit cardiac injury both acutely in ischemia/infarction, but also potentially in the chronic state of ongoing inflammation and injury, which characterizes heart failure. Although application in the clinic is not yet a possibility, already there are studies showing reduction in mitochondrial fragmentation and in infarct size in a rodent model. Thus this new field of mitochondrial fission and fusion has great potential to lead to new therapeutics to reduce cardiovascular morbidity and mortality. Although we have made enormous strides in the treatment of cardiovascular diseases, there remains need for new innovative treatment to further decrease the morbidity and mortality from these diseases.

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